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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 501714/MRO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. PCT/AU2003/001063	International Filing Date *(day/month/year)* 20 August 2003	Priority Date *(day/month/year)* 20 August 2002

International Patent Classification (IPC) or national classification and IPC

Int. Cl.[7] G01N 33/574, 33/66, H01J 49/40.

Applicant

PROTEOME SYSTEMS INTELLECTUAL PROPERTY PTY LTD *et al.*

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheet(s).

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of the report
17 March 2004	2 December 2004
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **NORMAN BLOM** Telephone No. (02) 6283 2238

INTERNATIONAL PRELI[redacted]ARY EXAMINATION REPORT

[redacted]ternational application No.
PCT/AU2003/001063

Basis of the report

With regard to the **elements** of the international application:*

[X] the international application as originally filed.

[ ] the description, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages , received on with the letter of

[ ] the drawings, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/fig.

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

I. **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	4, 6, 8-10, 12, 23-24, 28-29, 33-36	YES
	Claims	1-3, 5, 7, 11, 13-22, 25-27, 30-32	NO
Inventive step (IS)	Claims	4, 6, 8-10, 12, 23-24, 28-29, 33-36	YES
	Claims	1-3, 5, 7, 11, 13-22, 25-27, 30-32	NO
Industrial applicability (IA)	Claims	1-36	YES
	Claims	none	NO

2. Citations and explanations (Rule 70.7)

New citation: The Journal of Biological Chemistry (1982), **257** (21), 12752-12756, "Characterization of Human Melanoma-associated Ganglioside Antigen Defined by a Monoclonal Antibody, 4.2*", E. Nudelman *et al.*

The following documents cited in the ISR have been considered for the purposes of this report:

(D1) The Journal of Biological Chemistry (1986), **261** (27), 12796-12806,

(D2) The Prostate (1995), **27**, 187-197,

(D3) The Journal of Biological Chemistry (1992), **267** (27), 19248-19257,

(D4) The Journal of Biological Chemistry (2001), **276** (20), 16695-16703,

(D5) Analytical Biochemistry (1996), **242**, 8-14,

(D6) Analytical Biochemistry (1997), **248**, 63-75,

(D7) The Journal of Biological Chemistry (1994), **269** (29), 18794-18813,

(D8) Cancer Research (1988), **48**, 2125-2131,

(D9) Glycobiology (1995), **5** (1), 105-115,

(D10) Glycobiology (2000), **10** (6), 551-557,

(D11) WO 2002/008760.

Novelty (N) and Inventive Step (IS): Claims 1-36

D1 describes a structural analysis of *O*-linked oligosaccharides isolated from normal granulocytes, chronic myelogenous leukemia cells and acute myelogenous leukemia cells (i.e. granulocytic cells with three different degrees of maturation). These studies indicate that *O*-linked oligosaccharides of these cells utilise the same set of core structures although the ratio of each oligosaccharide is significantly different among the cells examined (page 12802 (discussion)). In AML cells a large proportion of *O*-linked oligosaccharides remain as Gal-(NeuAc-)GalNAc, in addition, a significant amount of the oligosaccharides has the structure of NeuNAc-Gal-(NeuNAc-)GalNAc (see page 12803 column 1 lines 11-16). Other parts of this document that are particularly pertinent are Table II (which tabulates the profile of *O*-linked oligosaccharides) and page 12803 column 2 lines 15-18, which indicates the use of these oligosaccharides as markers for oncogenesis. Oligosaccharides obtained by extraction of glycopeptides followed by alkaline borohydride treatment. Structural analyses were carried out using fast atom bombardment MS or GC MS following derivatisation. Claims 1-3, 5, 7, 11, 13-22, 25-27, 30, 31, at least, are considered to lack novelty and an inventive step in the light of this disclosure.

(continued)

I. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
P,X WO 2003/016464	27 February 2003	16 August 2002	17 August 2001

This document discloses a cancer specific oligosaccharide ((NeuNAc-)$_x$GalNAc-(Fuc-)$_y$GlcNAc- where x and y are ndependently 0 or 1) which is liberated from matrix metalloproteinase-9 by treatment with N-glycosidase F and analysed by MALDI-TOF MS. This citation is considered to be particularly relevant to the invention as defined by claims 1-7, 11, 13-18 and 35-36.

With regard to the document(s) listed in Box VI under "certain documents cited", these are documents published prior to the international filing date but later than the priority date claimed but which would otherwise be considered to be of particular relevance.

Under the PCT, novelty is considered only in respect of documents published before the priority date. The relevance of a document published after the priority date is dependent upon national law. Such documents are excluded from consideration in preliminary examination, under the PCT Guidelines but have been included here for information.

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 11 and 12 are not clear because the scope of "molecular species", referred to in step (iv), is far broader than glycans or glycoconjugates, which are isolated in steps (ii) and (iii), and includes other species present in the blood, sputum or saliva sample such as cytokines, DNA, hormones, peptides and proteins etc (see page 3 line 10 to page 4 line 6).

Claims 11 and 12 are not fairly based on the matter disclosed in the specification because they are not restricted to a comparison of the profile of glycans released from the glycoconjugates.

The claims are not clear as there are two claims numbered 31.

The description is not clear because there are two pages numbered 42 and two pages numbered 43.

Claim 20 is not clear as to whether the two sialic acid groups are linked together (see page 41 line 26) or whether the molecule merely contains two sialic acid moieties linked to the core oligosaccharide chain (for example see page 41 lines 5-6).

upplemental Box

To be used when the space in any of the preceding boxes is not sufficient)

Continuation of V. 2. Citations and explanations

D2 discloses the carbohydrate structure of Prostate Specific Antigen, a marker of prostate cancer, which has the oligosaccharide composition $\underline{NeuAc_2}Gal_2Man_3GlcNAc_4Fuc$. Claims 20 and 26-27 are considered to lack novelty and an inventive step in the light of this disclosure.

D3 discloses the structures of four major oligosaccharides isolated from a human rectal adenocarcinoma mucin. The structures of these oligosaccharides were considerably shorter and less heterogeneous in size than those reported in normal colonic mucins (see page 19248 the abstract and column 2 lines 20-29). Other pertinent disclosures contained in this document are the fraction FI-15 which discloses a $Hex_2HexNAc_2NeuNAc_2(SO_3H)$ oligosaccharide, fractions FII-4 and FI-6, both of which disclose $Hex_2HexNAc_2NeuNAc_2$ oligosaccharides, fraction FII-3 which discloses a NeuNAc-Hex-(NeuNAc-)HexNAc- oligosaccharide, fractions FI-6 and FI-7, both of which disclose $NeuNAcHex_2HexNAc_2$ oligosaccharides **etc**. The fraction FI-7 oligosaccharide having the structure corresponding to (v) of claim 19 (i.e. Hex-Hex-HexNAc-)HexNAc +NeuNAc). The oligosaccharide alditols were partially characterized by GLC-MS or FAB-MS. Claims 19-22, 25-27, 31, at least, are considered to lack novelty and an inventive step in the light of this disclosure.

D4 discloses an oligosaccharide marker for renal cell carcinoma having the structure GalNAc-(NeuNAc-)Gal-(NeuNAc-)GlcNAc-Gal-Glc (see the abstract) which was characterized in part using electrospray ionization MS. This oligosaccharide shows strong reactivity with two monoclonal antibodies (see page 16695 column 2). Claims 20-22, 26-27, 31-32, at least, are considered to lack novelty and an inventive step in the light of this disclosure.

The Journal of Biological Chemistry (1982), **257** (21), 12752-12756 discloses the cancer marker GD_3, having the structure NeuNAc-NeuNAc-Gal-Glc-Cer comprising two linked sialic acid residues. Claims 20-22, 26-27 and 31-32 are considered to lack novelty and an inventive step in the light of this disclosure.

Claims 1-3, 5, 7, 11, 13-22, 25-27, 30-32 are considered to be novel and inventive in the light of **D1, D2, D3, D4** and **The Journal of Biological Chemistry** (1982), **257** (21), 12752-12756 because no individual or obvious combination of these documents disclose all the essential features of these claims.

Claims 1-36 are considered to be novel and inventive in the light of the following documents cited in the ISR:

D5 discloses that altered glycosylation is a feature of many solid tissue diseases such as cancer. This document discloses finding that oligosaccharides are not adversely affected by fixation in formalin and storage in paraffin wax and hence archival tissues may be used to study the natural history of a disease such as cancer by liberation and structural characterization of oligosaccharides using techniques such as MALDI/MS.

D6 discloses oligosaccharide characterization and quantitation using 1-phenyl-3-methyl-5-pyrazolone (PMP) derivitization and MALDI-TOF MS. HPLC analysis of sialylated fetuin oligosaccharides released by PNG-F and derivatized with PMP revealed pseudomolecular ions corresponding to the major di- tri- and tetrasialylated oligosaccharides using MALDI-TOF MS.

D7 discloses a structural analysis of acidic oligosaccharides from CF individuals. Mucin glycopeptides were isolated from the sputum of CF patients. The carbohydrate chains were released by alkaline borohydride treatment, purified by ion-exchange chromatography, gel-filtration, and high performance anion-exchange chromatography. The structures of the oligosaccharide-alditols were determined by high resolution of ^1H NMR spectroscopy in combination with fast atom bombardment MS. It is indicated that "in the future, it will be necessary to determine whether or not some carbohydrate chains described in this study are specific for CF mucins" (see page 18813).

D8 discloses a carbohydrate epitope (Gal-(Fuc-)GlcNAc-Gal(Fuc-)GlcNAc-Gal-Glc, identified by fast atom bombardment MS (see the abstract)) associated with human squamous lung cancer.

(continued)

upplemental Box
To be used when the space in any of the preceding boxes is not sufficient)

ontinuation of V. 2. Citations and explanations

09 discloses the structures of the oligosaccharides released from four Normal faecal antigen-2 (NFA-2) samples by ydrazinolysis-nitrous acid deamination and electrospray ionization mass spectrometry. NFA-2 and carcinoembryonic ntigen (CEA) are considered as the same gene products and hence NFA-2 should be a normal counterpart of CEA roduced by colon epithelial cells of normal adults and fetuses, respectively (see the abstract). It is indicated that "the tructural alteration found in the sugar chains of CEA and its normal counterpart (NFA-2) in this study might be ffectively used for discriminating malignant CEA from its normal counterpart, and for improvement of the diagnostic alue of CEA in the future." (see page 112 column 2 lines 27-31).

010 discloses that the structure of the carbohydrate moiety of arylsulfatase A (ASA) from normal tissue is $Man_6GlcNAc(Fuc)GlcNAc$. Although it is indicated that the carbohydrate component of ASA synthesised in tumour issues and transformed cells undergoes increased sialylation, phosphorylation and sulfation (see the abstract), the recise structures of these glycan species do not appear to have been unequivocally established (se page 553 column 1).

011 discloses a method of identifying cancer markers the method comprising (i) separating a blood fraction from a uman or animal subject having cancer by mass spectrometry and (ii) separating a blood fraction from a healthy human r animal by mass spectrometry and comparing the profile of molecular species at (i) and (ii) and identifying those nolecular species having a modified level at (i) compared to (ii), wherein an enhanced or reduced level of said nolecular species indicates that the molecular species is a cancer marker. Although the cancer marker of this method nay be a glycoprotein (page 3 line 19), glycolipid or oligosaccharide (see claims 4 and 6), there is no suggestion that he blood is treated so as to release glycans from glycoconjugates which are separated from the sample (see page 18 lines 7-14, page 19 line 10 to page 20 line 22).

Industrial applicability (IA): Claims 1-36

Claims 1-36 are considered to possess industrial applicability in the area of biomedical testing.

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